PATENT
Customer No. 22,852
Attorney Docket No. 02481.1693

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	
HABERMANN et al.	Group Art Unit: 1653
Application No.: 09/664,326	Examiner: H. Schnizer
Filed: September 18, 2000	
For: SIGNAL SEQUENCES FOR PREPARING LEU-HIRUDIN BY SECRETION BY E. COLI INTO THE CULTURE MEDIUM	

Mail Stop Appeal Brief–Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

This is an appeal to the Board of Patent Appeals and Interferences ("the Board") from the final Office Action dated January 7, 2003 and the Advisory Action dated April 24, 2003, wherein claims 6, 7, and 9 have been rejected and claim 8 has been objected to. The appealed claims, as rejected, are set forth in the attached Appendix.

In support of the Notice of Appeal filed July 7, 2003 and pursuant to 37 C.F.R. § 1.192, Appellants present in triplicate this brief and enclose herewith a check for the fee of $330.00 required under 37 C.F.R. § 1.17(c). The brief is timely filed in view of the Petition for Extension of Time and fee filed concurrently herewith. If any additional fees

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are required or if the enclosed payment is insufficient, Appellants request that the required fees be charged to Deposit Account No. 06-0916.

I. Real Party In Interest

The real party in interest for this Application is Aventis Pharma Deutschland GmbH.

II. Related Appeals and Interferences

Appellant's undersigned legal representative knows of no other appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status Of Claims

Fourteen claims were presented for examination.

Claims 6-9 are pending in this application. Claims 6, 7, and 9 have been rejected and claim 8 has been objected to.

Claims 1-5 and 10-14 were cancelled in an Amendment after Final filed April 7, 2003.

IV. Status Of Amendments

All amendments have been entered. An Amendment after Final was filed in this application on April 7, 2003, wherein the Examiner entered the amendment, maintaining the rejection of claims 6, 7, and 9 and objecting to claim 8.

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V. Summary Of Invention

Hirudin is a highly-beneficial anti-coagulating protein derived from leeches. The present inventors have discovered that high yields of hirudin can be rapidly produced and secreted from *E. coli* bacteria, in part through the use of a suitable signal peptide (a small polymer of amino acids that assists a protein in being secreted from the cell).

The present invention relates to a process for selecting a signal peptide for secretory expression of a desired hirudin or hirudin derivative protein in *E. coli*. (Claim 6; spec. p. 5, ll. 22-21.) This process involves first expressing in *E. coli* a hirudin or hirudin derivative protein having antithrombotic effect and a defined amino acid at its N terminus. (Claim 6; spec. p. 5, ll. 23-25.) This amino acid is connected via its N-terminal to a test signal peptide. (*Id.*) The process next involves determining the expression rate (of the protein plus the signal peptide) by measuring the hirudin or hirudin derivative antithrombotic activity in the culture supernatant. (Claim 6; spec. p. 6, ll. 1-2.) These two steps are then repeated with various signal peptides, (claim 6; spec. p. 6, l. 3), and a desired signal peptide is selected by comparing the expression rates represented by the hirudin or hirudin derivative antithrombotic activity. (Claim 6; spec. p. 6; ll. 4-5.)

The present invention further relates to the process described above wherein the amino acid is leucine. (Claim 7; spec. p. 6, l. 11.) Finally, the present invention relates the process described above wherein the hirudin or hirudin derivative protein is hirudin. (Claim 9.)

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VI. Issue

The only issue on appeal is whether claims 6, 7, and 9 are patentable under 35 U.S.C. § 103(c) over Achstetter et al., 110 GENE 25-31 (1992), ("Achstetter") in view of EP 0 448 093 (for which U.S. Patent No. 5,919,895 is the English language counterpart) to Schmid et al. ("Schmid")[1].

VII. Grouping Of Claims

Each claim of this patent application is separately patentable, and upon issuance of a patent will be entitled to a separate presumption of validity under 35 U.S.C. § 282. For convenience in handling this appeal, however, claims 6, 7, and 9 stand or fall together.

VIII. Argument

The invention as presently claimed is in condition for immediate allowance. For all of the reasons discussed below, the outstanding rejection should be reversed and the application passed to issue.

The Examiner has rejected the claims under 35 U.S.C. § 103(a), contending that Achstetter discloses a method of selecting a signal peptide for secretory expression of hirudin or a hirudin derivative

> comprising (a) expressing in a culture medium, hirudin having antithrombotic activity, and which has a defined amino acid, aa_x, at its N terminus, wherein said amino acid aa_x, is connected via its N-terminal to a signal peptide to be tested; (b) determining the expression rate by measuring protein activity in the culture supernatant (c) repeating steps

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[1] U.S. Patent No. 5,919,895 ("the '895 patent") is the English language counterpart of Schmid and will be used herein when referring to the Schmid reference.

> (a) and (b) with various signal peptides; and (d) selecting the suitable signal peptide by comparing the expression rates represented by the hirudin antithrombotic activity found in step (b).

(June 27, 2002 Office Action at 8.) The Examiner admits, however, that Achstetter teaches expression of hirudin in yeast cells and does not teach or suggest expression in *E. coli*, as is required by the present claims.

The Examiner tries to make up for this deficiency with the secondary reference, Schmid, alleging that Schmid teaches that "the expression of hirudin in *E. coli* would be advantageous over processes known in the art using yeast . . . ." (June 27, 2002 Office Action at 9.) Specifically, the Examiner points to a single statement in Schmid, taken out of the context of the reference as whole, wherein Schmid states that "the cultivation of yeast cells takes longer and is more demanding than that of bacteria, for example, *E. coli*." (Schmid, '895 patent, col. 2, ll. 15-16.) The Examiner further alleges that Schmid teaches *E. coli* as the preferred bacteria "because of the availability of *E. coli* strains which show massive protein secretion into the culture medium." (June 27, 2002 Office Action at 9.)

Appellants respectfully request the Board reverse the rejection of the Examiner for at least the reason that the Examiner has failed to establish a proper *prima facie* case of obviousness. In order to establish a *prima facie* case of obviousness, the Examiner must show, among other things, a suggestion or motivation in the references or in the knowledge of one skilled in the art to modify the references or combine references teachings, along with a reasonable expectation of success. M.P.E.P. § 2143. This the Examiner has failed to do.

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The Examiner's case for obviousness is built upon the flawed rationale that one of ordinary skill in the art would have been motivated to combine the process of Achstetter in the vehicle (*E. coli* rather than yeast) of Schmid. Neither reference, however, contains any suggestion or motivation to modify or combine the reference teachings. In fact, the references teach away from such a combination. And moreover, even assuming *arguendo* such a combination were suggested, it is apparent from the face of the references that there would have been no reasonable expectation of success.

First of all, Achstetter does not contain any suggestion or motivation to use *E. coli* cells instead of yeast cells. Achstetter states that "[i]t was the aim of the present study to identify means to increase [hirudin] productivity in modifying the secretion signal(s)." (Achstetter, p. 26, ll. 28-30.) As one or ordinary skill in the art at that time would have known, and as Schmid clearly points out, "in *E. coli* cells, the yield is relatively low, and/or complicated isolation processes are necessary on disruption of the cells." (Schmid, col. 2, ll. 18-20.) Therefore, the prior art and the knowledge of those of ordinary skill in the art clearly *taught away from* using *E. coli* as a means for increasing the over yield of hirudin production.

The Examiner argues, however, that the Schmid reference itself teaches a process using *E. coli* that dramatically improves yield and simplifies isolation processes. (April 24, 2003 Advisory Action.) While this is true, the Schmid reference only overcomes the problems of *E. coli* by using *E. coli* secretor mutants, defined by the patent as specially cultivated *E. coli* strains that show massive protein secretion. (Schmid, '895 patent, col. 3, ll. 32-34.) In fact, the Examiner herself admits that *E. coli*

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in Schmid is only preferred because of the availability of the secretor mutant strains. (June 27, 2002 Office Action at 9, ll. 6-8.) The present suggestion by the Examiner for combining the references, however, would not necessarily include these *E. coli* secretor mutants. Rather, the Examiner suggests combining the system of Achstetter, including Achstetter's yeast signal peptides, not with the high-yield producing mutated *E. coli* of Schmid, but rather with non-mutated strains *E. coli* in general, which, as stated above, were known in the art to result in a low yield. Indeed, the present invention does not rely upon *E. coli* secretor mutants to obtain a higher yield.

Even if, assuming *arguendo*, such a combination were somehow suggested by the references, there was no reasonable expectation of success. One of ordinary skill in the art would have expected that by removing the *E. coli* secretor mutant strains from the invention of Schmid, one would simply be left with the same low-yield *E. coli* known in the art. There is simply no reasonable expectation in either of the references that practicing Achstetter's process in the prior art non-mutated *E. coli* of Schmid would result in the successful practice of the claimed invention.

Finally, the Examiner argues that the present claim language does not claim a specific signal peptide, and therefore Appellants cannot argue that Achstetter does not suggest combining its process (which includes the use of a yeast signal peptide rather than secretor mutants) with *E. coli*. In other words, according the Examiner, because Appellants do not claim the element, they may not argue that there is no motivation to combine that element with the secondary reference; therefore, the Examiner is free to use a combination including that critical element as the crux of her obviousness rejection.

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Such logic simply does not hold. Both references as a whole teach that in order to obtain a higher yield, one must use *either* yeast signal peptides (Achstetter, p. 26, ll. 7-10) *or E. coli* secretor mutants (Schmid, col. 3, ll. 32-34). The Examiner cannot advocate the removal of *both* and still assert a reasonable expectation of success. Likewise, the Examiner cannot assert the exclusion of one (secretor mutants) and inclusion of another (yeast signal peptides), as she must do to allege any reasonable expectation of success, absent some motivation to combine the two references. The fact that Appellants do not specifically claim yeast signal peptides is irrelevant to the analysis of whether or not there is, in the references themselves, any motivation or suggestion to combine references with a reasonable expectation of success: "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02(j).

In sum, Appellants respectfully request the Board to reverse the Examiner's obviousness rejection for at least the reason that no *prima facie* case of obviousness has been established. Appellants maintain that the Examiner has failed to establish a proper case of obviousness based on the cited references, taken alone or in combination, as there is no motivation or suggestion to combine or modify the references, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. Furthermore, such a combination of the references would not result in a reasonable expectation of success. Accordingly, Appellants respectfully request reversal of the rejection of the claims under 35 U.S.C. § 103(a).

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To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: October 24, 2003

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APPENDIX TO BRIEF ON APPEAL – PENDING CLAIMS

6. A process for selecting a signal peptide for secretory expression of a desired hirudin or hirudin derivative protein in *E. coli*, comprising:

(a) expressing in *E. coli* in culture medium, hirudin or a hirudin derivative which has antithrombotic activity, and which has a defined amino acid, aa_x, at its N terminus, wherein said amino acid is connected via its N-terminal to a test signal peptide;

(b) determining expression rate by measuring said hirudin or hirudin derivative activity in the culture supernatant;

(c) repeating steps (a) and (b) with various signal peptides;

(d) selecting said signal peptide by comparing the expression rates represented by the hirudin or hirudin derivative antithrombotic activity found in step (b).

7. The process of claim 6, wherein aa_x is leucine

9. The process of claim 6, wherein the desired hirudin or hirudin derivative protein is hirudin.

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